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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/44, 47/34

A1

(11) International Publication Number: **WO 97/26015**

(43) International Publication Date: 24 July 1997 (24.07.97)

(21) International Application Number: PCT/IB97/00014

(22) International Filing Date: 15 January 1997 (15.01.97)

(30) Priority Data:
08/584,320 16 January 1996 (16.01.96) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/584,320 (CON)
Filed on 16 January 1996 (16.01.96)

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUSTAINED RELEASE DRUG FORMULATIONS

(57) Abstract

A sustained release drug formulation including: a drug; a biodegradable polymer which is insoluble in water; and an oil vehicle in which both the drug and the polymer are dissolved. The oil vehicle contains 10-100 % by volume of a pharmaceutically acceptable oil and 0-90 % by volume of a pharmaceutically acceptable liquid carrier for the drug or the polymer.

SUSTAINED RELEASE DRUG FORMULATIONS

Background of the Invention

Biodegradable polymer sustained release formulations have been used to administer drugs over a prolonged period of time. See, e.g., U.S. Patent Nos. 3,773,919 and 4,767,628. These formulations are generally in the form of solid cylindrical implants, microcapsules, or microspheres. Solid implants require incisions in the patient which often are quite painful, resulting in poor patient compliance. Solid microcapsules and microspheres, which are injected into the patient, are often difficult to reproducibly manufacture and, thus, can give varying release profiles. Also, microcapsules and microspheres require lyophilization in order to avoid agglomerization of the particles during storage and large needles for injection.

Summary of the Invention

The invention features a sustained release drug formulation which includes: a drug; a biodegradable polymer insoluble in water (i.e., less than 0.01 mg/ml at 25°C);
and an oil vehicle containing 10-100% by volume a pharmaceutically acceptable and biodegradable oil and 0-90% by volume a pharmaceutically acceptable liquid carrier. The drug and the biodegradable polymer are dissolved in the oil vehicle.

The amount of a drug dissolved in an oil vehicle depends on its solubility, and may range from 1 to 500 mg per ml of the oil vehicle. The drug can be a peptide, e.g., somatostatin, luteinizing hormone-releasing hormone ("LHRH"), growth hormone releasing peptide, bombesin, gastrin releasing peptide, calcitonin, bradykinin,

The biodegradable polymer may be a liquid, or have a glass transition temperature or a melting temp rature up to 200°C. It may have a molecular weight (averaged) of 500-150,000 daltons, preferably, 1,000-75,000 daltons. Polymers with higher molecular weights slow down the release of the drug from the formulation. Generally speaking, 1-500 mg (preferably, 15-300 mg) of the polymer can be dissolved in 1 ml of the oil vehicle.

Examples of a biodegradable oil, an essential component of the oil vehicle, include oils derived from plants (e.g., corn oil, coconut oil, linseed oil, olive oil, palm oil, sunflower seed oil, cottonseed oil, peanut oil, sesame oil, or castor oil), animals (e.g., sardine oil, cod-liver oil, whale oil, sperm oil), paraffin oil, or triglyceride derivatives such as miglyol (Labafac, Gattefusse, Lyon, France), or mixtures thereof.

The oil vehicle may also contain one or more pharmaceutically acceptable liquid carriers, e.g., solvents of either the drug or the polymer such as water and ethanol. The amount of a carrier added should remain miscible with the oil used to form the vehicle. If necessary, a pharmaceutically acceptable liquid ester or polyether may be added to the oil vehicle to aid in the dissolution of the drug or the polymer into the oil vehicle. Examples of suitable esters include benzyl benzoate (which can assist the dissolution of the polymer such as a polyester), or polyethylene glycol, e.g., PEG 400 (which can assist the dissolution of the drug such as a peptide). The ester or polyether may constitute 0.1-90% by volume of the oil vehicle.

The oil vehicle may also include a pharmaceutically acceptable surfactant in order to clarify the formulation. Examples of suitable surfactants include polysorbates (e.g., TWEEN 80 or SPAN 80).

Thus, what is meant by "an oil vehicle" herein is a water-immiscible medium in which a drug and a

patent applications, patents, and other references mentioned herein are incorporated by reference.

Example 1

In a 100 ml beaker, 6 ml of benzyl benzoate and 8 ml of polyethylene glycol 400 (PEG 400) were mixed together. 6 ml of sesame oil was then added to and mixed within the beaker, forming an oily substance. The oily substance was then mixed with 50 mg of a biodegradable polymer and was added to the same beaker and dissolved by heating the beaker to 60°C while stirring. The beaker was then cooled. 10 mg of blue patente V dye (Prolabo, Fontenay Sous, Bois, France; used here as a drug substitute for experimental purposes) dissolved in 0.1 ml of water and 0.1 mg of TWEEN 80 dissolved in 0.9 ml of ethanol were mixed with the oily substance to form the sustained release formulation. The biodegradable polymer was a copolymer comprising 50% by weight D,L-lactic acid and 50% by weight glycolic acid ("50/50 PLGA") and having an average molecular weight between 20,000 and 30,000 daltons, and was synthesized using standard methods known in the art. See, e.g., U.S. Patent Nos. 2,703,316 or 2,758,987.

2 ml of the resulting sustained release formulation was poured into a vial containing 20 ml of distilled water. The oil settled at the bottom of the vial and formed an emulsion. Upon agitation with a magnetic stirrer, the emulsion formed globules. The blue dye remained in the emulsion globules and was slowly released into the surrounding water over time. The subsequent addition of 3 ml of methylene chloride to the vial, a solvent of the copolymer, degraded the emulsion and quickly release the blue dye into the distilled water.

days by sinus retroorbital taking. 50 µl of blood sample, 200 µl of I^{125} testosterone, and 200 µl of antiserum were poured into tubes which were shaken and incubated during 24 hours at 37°C. The immuno-precipitant reagent propanol (1 ml) was added in each tube, and all the tubes were incubated 15 minutes at room temperature. The supernatant was eliminated after centrifugation, and radioactivity was measured with a multigamma counter LKB-WALLAC Model 1261 (LKB, Les Ulis, France).

The data is presented in Table I. As the data indicated, the formulation continuously release the LHRH agonist over a period of at least 29 days as indicated by the inhibition of testosterone in the rats.

TABLE I

DAYS	TESTOSTERONE (ng/ml)
0	2.80
2	4.17
4	0.47
8	0.64
11	1.34
15	1.04
18	0.69
22	1.63
25	1.57
29	0.85

Example 5

The above synthetic protocol in Example 3 was performed with the exception that 62 mg of the insoluble pamoate salt of Triptorelin™ dissolved in 1 ml of ethanol was used instead of 51 mg of the acetate salt of Triptorelin™ dissolved in 0.1 ml of water and 0.9 ml of

added to the same beaker to form the sustained release formulation.

Example 7

The formulation described in Example 6 was intramuscularly injected into Wistar rats at a dose of 6 mg of peptide per kg weight of rat. Blood for peptide analysis was collected into aprotinine tubes to avoid any peptide degradation (Laboratoire CHOAY, Gentilly, France). Samples were centrifuged immediately and the plasma separated and stored at -20°C until radioimmunoassay ("RIA") to determine the amounts of the drug (ng/ml). RIA had been developed after immunization of rabbits with peptide conjugated to bovine serum albumin to obtain a specific antibody. Iodine 125 has been used to label LANREOTIDE.

The data is presented in Table III. The formulation slowly released LANREOTIDE over a period of at least 12 days.

TABLE III

DAYS	LANREOTIDE (ng/ml)
2	9.31
5	1.87
8	0.81
12	0.28

Example 8

The above synthetic protocol in Example 6 was performed with the exception that 365 mg of the acetate salt of LANREOTIDE dissolved in 0.1 ml of water and 0.9 ml of ethanol was used instead of 388 mg of the pamoate

Example 10

The formulation described in Example 9 was intramuscularly injected into Wistar rats at a dose of 4 mg/kg. The concentration of the steroid was determined using an EIA (enzymoimmunoassay) kit (Cayman Chemical, SPI-BIO, Massay, France). The data is presented in Table V. The formulation slowly released the 17β-hydroxy-oestradiol over a period of at least 11 days.

TABLE V

DAYS	17β-HYDROXY-OESTRADIOL (ng/ml)
2	12.45
4	2.62
8	0.19
11	0.10

Example 11

10 ml of PEG 400 and 8 ml of benzyl benzoate were added to and mixed within a 100 ml beaker. 1 g of 50/50 PLGA copolymer having an average molecular weight of 40,000 to 50,000 was then added to the same beaker and dissolved by heating the beaker to 60°C while stirring. The beaker was then cooled. 200 mg of progesterone was then added to and mixed within the beaker. 4 ml of castor oil was then mixed with 2 ml of ethanol and slowly added to the same beaker to form the sustained release formulation.

CLAIMS

1. A sustained release drug formulation. said formulation comprising:

a drug:

a biodegradable polymer which is insoluble in water; and

an oil vehicle containing a pharmaceutically acceptable oil which is biodegradable and a pharmaceutically acceptable liquid carrier which dissolves said drug or said polymer. said oil and said carrier constitution 10-100% and 0-90% by volume of said oil vehicule. respectively;

wherein both said drug and said polymer are dissolved in said oil vehicle.

2. A formulation of claim 1. wherein the amount of said polymer is 1-500 mg per ml of said oil vehicle.

3. A formulation of claim 1 or 2. wherein the amount of said polymer is 15-300 mg per ml of said oil vehicle.

4. A formulation according to anyone of claims 1 to 3. wherein the molecular weight of said polymer is 500-150.000 daltons.

5. A formulation according to anyone of claims 1 to 4. wherein said polymer is made of a monomer selected from ε -caprolactone. lactic acid. glycolic acid. and a combination thereof.

6. A formulation according to anyone of claims 1 to 5. wherein the molecular weight of said polymer is 1.000-75.000 daltons.

7. A formulation according to anyone of claims 1 to 6. wherein said oil is corn oil. cottonseed oil. peanut oil. sesame oil. castor oil. or a mixture thereof.

8. A formulation according to anyone of claims 1 to 7. wherein said oil vehicle further comprises a pharmaceutically acceptable ester or polyesther to facilitate dissolution of said drug or polymer. said ester or polyether constituting 0.1-90% by volume of said oil vehicle.

9. A formulation according to claim 8. wherein said ester or polyether is benzyl benzoate, polyethylene glycol. or a mixture thereof.

International Application No
PCT/IB 97/00014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/44 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 9210 Derwent Publications Ltd., London, GB; Class A96, AN 92-075205 XP002028258 & JP 04 018 035 A (NKK CORP) , 22 January 1992 see abstract ---	1-14
Y	US 3 773 919 A (BOSWELL G ET AL) 20 November 1973 cited in the application see column 9, line 55 - line 64 see column 11, line 38 - line 46 --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 March 1997	16. 04. 97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 97/00014

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